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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,129	06/28/2002	Jussi Kauhanen	2630-114	1660

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 04/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,129	KAUHANEN ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 1/24/05 have been entered. Claims 1 and 2 are pending. Applicant's arguments have been carefully considered but are not persuasive. The arguments are addressed following the statement of rejection. This action is **FINAL**.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1 and 2 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

The claims are drawn to methods for diagnosing a susceptibility for having a risk for development of alcoholism, wherein the method comprises a single step of determining whether the person has a polymorphism in signal peptide part of the human preproNPY, wherein the polymorphism comprises a substitution of proline for leucine at position 7 in the signal peptide, said polymorphism being indicative of a risk for the development of alcoholism. The nature of the invention, thus, relies on an association between the presence of a polymorphic form of the human preproNPY wherein there is a proline at position 7 of the signal peptide and a risk for the development of alcoholism. The claim suggests that the person who has the proline at position 7

of the signal peptide of the human preproNPY have a greater likelihood of developing alcoholism than those that do not have this polymorphic form.

Breadth of the Claims

The claims are limited to the detection of a specific polymorphism within a nucleic acid sample via analysis of the nucleic acid. The detection of the presence of a particular allele of the polymorphism is "indicative of a risk for the development of alcoholism in said person."

State of the Art

The prior art teaches the detection of the polymorphism at position 7 in the signal peptide via analysis of nucleic acid sequence and that this polymorphism may be associated with seizures in alcohol withdrawal (see, for example, Okubu *et al.* as cited in the IDS). The prior art does not provide any suggestion or evidence to support an assertion that either allele of this polymorphism is associated with increased likelihood of developing alcoholism.

The prior art teaches that for men moderate drinking is defined as no more than two drinks per day, with a standard drink being 12 grams of pure alcohol (See for example, The Physician's Guide to Helping Patients with Alcohol Problems).

Teachings of the Specification and Working Examples

The experimental section of the specification describes a study in a cohort of men were questioned about their level of alcohol use and the average weekly consumption of alcohol was calculated for each subject. Further, the proportion of heavy users consisting of those whose average daily consumption exceeded 3 standard doses was calculated (p. 13, lines 15-25). The genotype of these men was determined using RFLP analysis (p. 14, lines 20-28). The proportion

of heavy drinkers in the genotype groups was compared using a chi-square test, with P-values less than 0.05 interpreted as being statistically significant (p. 15, lines 6-9).

The specification teaches that the proportion of heavy users was higher among men with the proline allele, but this difference was not a significant difference (p=0.10; p. 16, lines 5-8). Table II shows the alcohol consumption in grams of ethanol per week, and shows that the group of men with the proline allele had a higher mean weekly alcohol consumption in pure ethanol (115 g/wk versus 86 g/wk; p=0.03; p. 17). However, it is significant to note that even the level of alcohol consumption observed for the proline allele carriers falls within the defined level of "moderate drinkers" since an average of 115 g/week of alcohol averages to less than two drinks per day. The physician's guide includes this level of drinking as "low-risk drinking." Thus, while the specification demonstrates that there is a difference between the amount of alcohol consumed for proline allele carriers versus non-carriers, the specification fails to demonstrate a link between the allele and heavy drinking, high risk drinking or alcoholism.

There is no analysis in the specification of men or women who were diagnosed as alcoholics.

Level of Unpredictability

The establishment of an association between a polymorphism and a give phenotype is an entirely empirical science, and indeed is highly unpredictable. The instant specification failed to show an association between heavy drinking and the polymorphism. The only association that was demonstrated showed that the mean alcohol consumption of Pro7 allele carriers was higher than that of non-carriers, but significantly, BOTH mean consumption levels were within the range of low risk consumption for men. An association observed in an initial study is frequently

not supported in subsequent studies. This unpredictability is highlighted in the post filing date art concerning the putative association between the polymorphism of the instant application and alcoholism.

Ilveskoski et al. teach that the Pro7 allele might not predispose to alcoholism, but instead might retard the transition from social drinker to alcoholism (Alcoholism, clinical and experimental research, October 2001, 25(10) 1420-1422). Lappalainen et al. report that the frequency of the Pro7 allele was significantly higher in alcohol-dependent samples than in controls (Archives of General Psychiatry, September 2002, p. 825-831; see p. 828). In a study to follow-up that of Lappalainen et al., Zhu et al. teach that Pro7 frequencies were not significantly different in alcoholic and control populations (Alcoholism, Clinical and Experimental Research, January 2003, Vol. 27, No. 1, p. 19-24). Further, they conducted a meta-analysis wherein they found that the Pro7 frequency was the same in Caucasian alcoholics and Caucasian controls. Zhu et al. conclude that Pro7 is not associated with diagnosis of alcoholism in Caucasian populations. These studies demonstrate the high degree of unpredictability with regard to determining an association between this allele and alcoholism in particular. Even many years after the instant invention, there is no clear answer in the literature as to whether carrying the Pro7 allele results in an increased predisposition for development of alcoholism.

Conclusion

The instant specification does not provide any evidence which definitely demonstrates that carriers of the proline allele would have a higher likelihood of becoming alcoholics. The specification only demonstrates that carriers of the allele have an increased likelihood of

consuming alcohol at a mean level that is higher than non-carriers, but both levels are low risk levels.

Thus, having considered all of these factors, particularly the absence of working examples, teaching in the specification and prior art, and high degree of unpredictability, it is concluded that it would require undue experimentation to practice the claimed invention.

Response to Remarks

Concerns regarding the detection of the polymorphism in polypeptides have been removed from the rejection as methods which detect the polymorphism within polypeptides are no longer within the scope of the claims.

The central issue with regard to the enablement of the instantly claimed invention, therefore, is whether or not the specification provides a reliable association such that the detection of the allele encoding praline at position 7 in the signal peptide part of human preproNPY is "indicative of a risk for the development of alcoholism" in a person, as such an association is critical for the practice of the claimed invention. As summarized in the rejection, the specification does not provide such an association, which is notable in light of the highly unpredictable art area.

Applicant traverses the rejection, stating that the examiner is in error with respect to the sufficiency of the data in the specification. Applicant points to a showing in the specification that the presence of proline7 was associated with an approximately one-third higher average consumption of alcohol than subjects without the allele. This finding is presented in the specification at page p. 16, lines 5-8. Applicant argues at the bottom of page 8 of the response that p-value is only a probability for estimating the significance of the difference, not the

probability for estimating the observed difference between the means and that sometimes different probability levels are used instead of p=0.05. This being the case, the p-value nonetheless represents an estimate of the probability that the difference observed between test and the control is not due to random chance, and generally in the scientific community p=0.10 is considered too high to draw reliable conclusions. The results were not considered significant by applicant's standard set forth in the specification since p=0.10, as Applicants teach in the specification that "P-values less than 0.05 obtained from the statistical tests were interpreted as statistically significant (p. 15, lines 6-8)." The arguments to the contrary in the response are not consistent with the very clear teaching in the specification regarding the level necessary to consider a showing "statistically significant," and are considered to be attorney arguments that are not evidence on the record. Attorney arguments do not substitute for evidence on the record (see MPEP 716.01(c)). At the top of page 5, applicant states that applicants initial findings were supported by a study Lappalainen et al. Applicant is reminded that the post-filing date art cannot be used to establish that the specification was enabled at the time the application was filed. Therefore these references do not support applicant's arguments that the specification was sufficient to enable the claimed invention at the time of filing since MPEP 2124 states,

> "...it is impermissible to use a later factual reference to determine whether the application is enabled or described as required under 35 U.S.C. 112, first paragraph. In re Koller, 613 F.2d 819, 823 n. 5, 204 USPQ 702, 706 n.5 (CCPA 1980). References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made. Ex parte Erlich, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992)."

The post-filing date references used in the rejection are set forth to demonstrate the high level of unpredictability in the related art area, thus supporting the examiner's statement that the

establishment of an association between a phenotype and a polymorphism is an entirely empirical technology. Applicant states in the response that there are two positive, accordant reports of an association between proline7 and alcoholism, versus one post-filing negative teaching (remarks, p. 5, bottom ¶). However, one the two reports that support the instant filings, Kauhanen et al., is written by a research group which includes the instant inventors and presents the exact same data presented in the instant application. Notably, in that paper, however, Kauhanen et al. never suggest that the allele is predictive of alcoholism per se, and instead always discuss an association between the allele and "alcohol consumption" or "alcohol use." They conclude their paper by stating that "If replicated in further studies, these findings may have significant clinical and public health implications (p. 120)," supporting the idea that the data they present are not sufficient to drawn definite conclusions concerning alcoholism. Instead, since the art area is highly unpredictable, the data require further support and confirmation before they would become useful for making patient predictions.

Regarding the teachings of Ilveskoski et al., applicant states that the study is "biased" and thus concludes that it is irrelevant (first full sentence p. 6 of response). Applicant criticizes the study because the control population had a proline7 substitution frequency reported to be roughly double that of the general Finish population. This is not persuasive. Ilveskoski et al. specifically address this finding in their discussion stating that the reason for the difference "is not clear" but go on to state "On the basis of these results, it seems, however, quite unlikely that even a larger sample of alcoholics would prove the original hypothesis of increased susceptibility of alcoholism among Pro(7) carriers. However, it could also be possible that the differing results from the two studies are fortuitous (i.e., no association), and NPY many not contribute to either

finding (p. 1421, 2nd column)." Further, Ilveskoski et al. point out that all of the studies are dealing with two different traits, heavy alcohol consumption and alcoholism, explaining that high daily alcohol consumption does not mean a person meets the diagnostic criteria for alcoholism.

Applicant criticizes the sample size used by Ilveskoski et al. However, it is notable that even with the smaller sample size there was sufficient observed difference between the populations to establish a relationship between the genotypes of controls and alcoholics at a level of $p<0.05$ for all measures comparing alcoholics and controls. Notably, this effect was opposite that set forth in the instant claims, there was a higher frequency of the pro(7) genotype among controls than alcoholics. The teachings of Ilveskoski et al. thus are supportive of the examiner's statements regarding the high level of unpredictability in this technology.

The comments regarding Drube et al. have been removed from the rejection in view of applicant's requirement that the study population itself be heterogenous for the polymorphism.

Finally, applicants dismiss the teachings of Zhu et al. because according to applicant Zhu et al. "haven't carefully enough studied the paper by Ilveskoski et al. (response p. 7, first full ¶)." This dismissal is simply an attorney argument with no factual basis in the paper by Zhu et al. It is not persuasive.

Thus, having carefully considered all of applicant's arguments, the rejection is MAINTAINED.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

April 12, 2005